A RECEPTOR INDEPENDENT 4D-QSAR STUDY ON HIV-INTEGRASE INHIBITORS BY MEANS OF LQTA-QSAR SOFTWARE

Eduardo Borges de Melo[1,2]; *Márcia Miguel Castro Ferreira*[2]

[1]Curso de Farmácia - Universidade Estadual do Oeste do Paraná (Unioeste) Brasil - http://www.unioeste.br;
[2] Chemistry Institute, University of Campinas (Unicamp) Brasil - http://lqta.iqm.unicamp.br;
e-mail: marcia@iqm.unicamp.br

In spite of the implementation of HAART, there is a continuous need to search for new anti-HIV agents. The computer aided-drug design (CADD) related methods are the main approach used for the research of this class of drugs. In this work, the new 4D-QSAR methodology[1] , named LQTA-QSAR, is applied to a set of 85 HIV-IN inhibitors having the ß -diketo acid (DKA) pharmacophoric substructure in common. Geometry optimizations were carried out at B3LYP/6-31G** level and ChelpG charges calculated using Gaussian. Ionic states of compounds at pH 7.5 were determined by Marvin (74 anions and one cation), and several properties were calculated for all compounds. GROMACS software was used for molecular dynamics, MD, simulations and generating the conformational ensemble profile. LQTA-QSAR method was used for calculating intermolecular interaction energies at each grid point, using two different probes and all aligned conformations from MD simulations. The probes used were: Zn^{+2} to explore possible interactions with the metallic co-factor, and Ar(C-H) for hydrophobic interactions. The OPS method[2] was applied for variable selection in the construction of the PLS model. In addition to external validation, the QSAR model was validated by leave-*N*-out cross-validation and y-randomization. The best model (n=75; outliers: 10; R^2 = 0.83; SEC= 0.39; F(7,67)= 39.26; Q^2_{LOO} = 0.71; SEV = 0.47; R^2_{pred} = 0.74; SEP= 0.53; ARE_{pred} = 6.66%; k= 0.99; k'= 0.99; $|r^2_0 - r'^2_0|$= 0.19) was built with 15 descriptors. Visualization of descriptors in the 3D space indicates that they can be related with the metallic co-factors necessary for the enzymatic and inhibition activity, with possible interactions in the hydrophobic pocket and with some accessory interactions at the HIV-IN active site. The good statistics of the model, its robustness and relation with the inhibition mechanism, support the applicability of this model in the proposition of new active compounds.

References

[1] Martins JP; Barbosa E; Pasqualoto KF; Ferreira MMC, LQTA-QSAR: a new 4D-QSAR methodology. *J. Chem. Inf. Comput. Mod.* 2009, in press.

[2] Teófilo RF; Martins JP; Ferreira MMC, Sorting variables by using informative vectors as a strategy for feature selection in multivariate regression. *J. Chemometr.,* 2009, 23, 32.

Acknowledgements: FAPESP